Pancoast Tumors are another subgroup often requiring Trimodality Rx. In SWOG/ INT 0160 induction chemoXRT were given followed by resection. 111 eligible patients who were med negative including T3-4 / N0-1. 80 (72.1%) were T3; 31 were T4 tumors. 2 cycles of cisplatin/ etoposide W/ 45 Gy of radiation were given. There were 3 treatment deaths (2.7%). 95 pts were eligible for surgery (85%); 83 underwent thoracotomy (75%) 2 (2.4%) died postoperatively. 76 (92%) underwent complete resection. 54 (65%) specimens showed complete/partial response. 2-year survival was 55%; 70% survival if complete resection was achieved. Finally, the role of high dose trimodality therapy for Superior Sulcus tumors was studied by Kwong KF, Gamliel Z, Krasna MJ. 36 patients with Pancoast tumor Stage IIB-IV (solitary brain met) were treated. R0 resection was achieved in 36 (97.3%) patients. Operative mortality was 2.7% (n = 1). High-dose radiotherapy (mean 56.9 Gy; range, 30-70.2 Gy) was successfully tolerated in all but 1 patient. Pathologic complete response was found in 40.5% (n = 15) of patients.

Session M02: Translational Research in Radiation Oncology

M02-01 Translational Research in Radiation Oncology, Mon, Sept 3, 10:30 - 12:00

FDG-PET and tumor response

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Introduction: Structural imaging using CT scanning has long been the standard investigation for response assessment after chemotherapy, neoadjuvant chemoradiation or definitive radiation therapy (RT) for both non-small cell (NSCLC) and small cell lung cancer (SCLC). Changes in tumor dimensions after therapy are categorized into the widely-used WHO and RECIST response categories, which have prognostic significance. However, CT scanning suffers from well-known limitations. These limitations include the relatively slow rate of change often observed in tumor volume after effective therapy, dependence on the unreliable parameter of lymph node size to determine involvement by tumor and an inability to distinguish between inactive scarring or necrotic tumor and active tumor in residual masses after therapy. The utility of CT may be further reduced by the presence of radiation pneumonitis and atelectasis, which can make it impossible to measure tumor size.

Increasing numbers of studies demonstrate that functional imaging with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can be more accurate for early assessment of response to treatment of NSCLC than structural imaging. FDG is a glucose analogue that is taken up and trapped at a high rate by malignant tumor cells, especially those of NSCLC. After intravenous injection of FDG labeled with the positron emitting isotope 18F, most lung cancers can be imaged using a PET scanner. Changes in FDG uptake after therapy may precede changes in tumor volume and therefore, comparison of pre and post therapy PET scans can provide an early semiquantitative indication of response.

FDG-PET Response Assessment Methodology

Therapeutic response information provided by PET is more complex than that provided by structural imaging and researchers continue to search for the best way to use it. Uptake of FDG into tumors is influenced by many different biological factors, including substrate utilization, tumor perfusion, effects of hypoxia and apoptosis , the viable cell fraction, the extent of inflammatory cell infiltrate and oncogene expression. PET scanning allows the investigator to visualize and measure the intensity of residual metabolic activity within a lesion as well as estimating its size, especially if PET/CT is used rather than PET alone. The feature that really distinguishes PET from structural imaging is its ability to integrate the effects of residual tumor volume and residual tumor metabolic activity into a single response assessment. The best methodology for determining early PET response has not yet been established but there are two main approaches.

Visual /Qualitative Methods

After definitive therapy, a visual estimate of response can give extremely useful prognostic information. This method is simple and widely-used, especially in the lymphomas. It relies on the skilled perceptions of an experienced human observer and compares metabolic activity in all lesions when pre- and post-treatment PET scans, performed under identical conditions, are displayed side by side. Absence of residual uptake of FDG, or reduction in intensity of uptake to no more than that contained in the blood pool, denotes a complete metabolic response or CMR. An appreciable reduction in the intensity of uptake, in the absence of any new lesions, is denoted as a partial metabolic response or PMR. Progressive metabolic disease, or PMD, denotes any site of progression and if there is no appreciable change the term stable metabolic disease (SMD) is used.

Semiquantitative or SUV-based Methods

There are very many possible methods for quantitative assessment of response to therapy based on PET 1, ranging from the simple to the extremely complex. None of the more complex methods has been widely adopted and the only parameter with widespread acceptance as a semiquantitative measure of lesion intensity is the standardized uptake value or SUV. The most commonly used SUV parameter is the SUVmax, derived from tissue activity at a single point in time and using the pixel with highest lesion activity. This analysis is not dependent on acquisition of dynamic information of the type required for kinetic modeling approaches. SUV measurement is affected by a variable time between injection and scan, by variation in time to equilibrium and by variation in uptake curve slope before and after therapy. Additionally it may be affected by blood glucose concentration, differs if weight or body surface area is used as a correction factor and may not give the same results if different scanners used. Additionally, inflammatory reactions (infection, radiation) in normal tissues may produce SUV in "malignant" range (SUV > 2.5). However, the absolute accuracy of the SUV measurement may not be a confounding factor in assessment of treatment response using FDG-PET if the pre- and post-treatment scans are performed on the same scanner under identical conditions. This type of assessment may give the earliest measure of response and be the best available method for determining response to chemotherapy or to neoadjuvant therapy when insufficient time has elapsed for responses to evolve fully after therapy.

Clinical studies of PET response in NSCLC

PET Response after definitive Radiation Therapy/Chemoradiation

Data from prospective studies at Peter MacCallum Cancer Centre have shown that PET is superior to CT in response assessment after chemoradiation for NSCLC. PET and CT responses were identical in only 40% of cases 2. Additionally, PET response was correlated powerfully with survival and patterns of failure 3. Pre- and post-treatment FDG-PET scans were compared for 88 patients after concurrent platinum-based radical chemo/RT (n=73) or radical RT alone (n=15). Follow-up

PET was performed at a median of 70 days after treatment. PET responses were; CMR n=40 (45%), PMR n=32 (36%), SMD n= 5 (6%) and PMD 11 (13%). Median survival for CMR and non-CMR patients was 31 and 11 months respectively (P=0.0001). One year survival for CMR and non-CMR patients was 93% and 47% respectively and 2 years survival was 62% and 30% respectively. Attainment of CMR after radical RT/chemoRT for NSCLC bestowed superior freedom from both local and distant relapse. Other series have reported a strong correlation between PET response and outcome. Increased FDG uptake can be observed due to inflammation in normal tissues after RT, but with careful interpretation this does not prevent accurate response assessment. Recent pilot studies suggest that PET response measured during a course of RT has prognostic significance and could potentially be used to dynamically modify RT target volumes or refine dose distributions to target the more resistant tumor regions.

PET response after Neoadjuvant Therapy

Several trials have investigated the correlation between early PET response to neoadjuvant chemotherapy 4, 5 or chemoRT 6 prior to surgery and histopathological response and/or survival. There have been conflicting reports of the utility of this information, but a strong but imperfect correlation between PET findings and histopathological response exists. PET information could potentially be used to select patients for surgery and at the very least could exclude those who have disease progression from unnecessary aggressive therapy.

PET response after Chemotherapy in advanced NSCLC

Because FDG PET scans can give an indication of response long before there are conclusive changes on CT scans, the use of PET to assess early response to chemotherapy in advanced NSCLC has seemed an attractive idea. Indeed there is evidence that a significant early reduction in the SUV has prognostic significance 7. PET is becoming more widely used in clinical trials to test investigational agents for activity. It may be used in routine clinical practice to allow an early change in chemotherapy or cessation of treatment in patients who show no signs of a useful response. This may prevent unnecessary toxicity in patients who would otherwise receive multiple cycles of chemotherapy before CT could show that treatment was ineffective.

Conclusions

As PET scanning becomes more widely available and accessible, it is likely to become the investigation of choice for response assessment in NSCLC in a wide range of clinical situations.

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M02-02 Translational Research in Radiation Oncology, Mon, Sept 3, 10:30 - 12:00

Update of EGFR inhibitors and radiation in the management of non-small cell lung cancer...where do we go next?

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Exciting new therapeutic approaches for locally advanced lung cancers has been realized recently through a greater understanding of the cancer cell signaling pathway. Therapeutic agents designed to disrupt critical components of the growth factor signaling pathway such as the epidermal growth factor receptor cascade have demonstrated response rates of approximately 10% in patients with chemo-refractory lung cancers. The JBR-21 trial provided level 1 evidence that even as monotherapy, Tarceva, an EGFR TKI, improved survival in patients with stage IV NSCLC patients who progressed following chemotherapy (1). Where are we with targeted therapies and radiation in the management of non-small cell lung cancer? Preclinical data confirmed that blockade of the EGFR pathway would enhance the cytotoxic effects of ionizing radiation (2). This was a rationale hypothesis since radiation appears to amplify EGFR signaling (3) along with other aspects of the cancer survival process including angiogenic proteins such as vascular endothelial growth factor (VEGF). Recent randomized trials have confirmed the efficacy of combining an EGFR inhibitor, cetuximab, with radiotherapy in patients with locally advanced head and neck cancer (4).

How can we tell who will respond to EGFR inhibition? Clinical data has emerged recently to assist in predicting responders versus non-responders to small molecule EGFR-TKIs. Specific characteristics that appear to be related to response to EGFR-TKIs include mutations to the EGFR domain as well as specimens that are both IHC and FISH positive for gene amplification of the EGFR (5-9). Regarding the former, data emerged over the past several years that correlated mutations in the EGFR TK domain to gefitinib-responsiveness in NSCLC. Interestingly, a majority of mutations in EGFR have been observed primarily in the Asian population and similar findings have been seen in erlotinib-sensitive patients. We also are aware that mutations are more common in never-smokers, women, Asians, and patients with adenocarcinoma, likely explaining the association of these characteristics with TKI response. Interestingly, there is a paucity of data correlating mutations, or FISH positivity to response to monoclonal antibodies against the EGFR. Pre-clinical information has shown that epithelial to mesenchymal transition plays a role in correlating response to erlotinib in NSCLC and we have seen that in head and neck cancer as well to gefitinib (10-11).

Currently, there are several clinical trials combining EGFR inhibitors with radiation in lung cancer. The RTOG (0324) has recently completed a Phase II trial combining chemo-radiation with cetuximab in locally advanced, stage III NSCLC. Ninty-three patients were entered and 87 patients were analyzed. At ASCO 2007, early results from this study indicated that it was reasonably well tolerated (12). With a median follow-up of 14 months a response rate of 62% (n=54) was observed with a 12 month overall survival (OS) of 68%. Adverse events related to treatment include 20% of patients with grade 4 hematologic toxicities and 7 patients with grade 3 esophagitis. Three patients reportedly died of pulmonary complications (adult respiratory distress syndrome,

